

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 2, 27-29, 32-41, 43, 45-47, 49, 50, 52, 53, 78-80, 84-93, and 96 are pending in the application, with 1, 46, 49, and 52 being the independent claims. Claims 30, 31, 48, 54, 60, 82, 83, and 97 are sought to be canceled without prejudice to or disclaimer of the subject matter therein solely to expedite prosecution. Claims 1, 32-34, 52, 53, and 88-93 are sought to be amended. Support for the amendments to claims is found in the claims as originally filed. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Supplemental Amendments

The Office Action mailed July 3, 2007 indicates that the Office Action is in response to the communication filed April 2, 2007. Applicants point out that supplemental amendments were filed June 12, 2007 and June 22, 2007. Applicants respectfully request that these supplemental amendments be considered by the Examiner prior to the mailing of the next communication from the USPTO.

Information Disclosure Statements

The Office Action mailed July 3, 2007 did not include an initialed copy of the PTO-1449 form submitted with the Information Disclosure Statement filed June 20, 2007. Applicants respectfully request that the Information Disclosure Statement be considered and an initialed copy of the PTO-1449 form be included with the next communication from the USPTO.

Rejections under 35 U.S.C. § 112

Claims 1, 2, 27-41, and 43-45 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the cancers demonstrated in the examples in the instant specification, allegedly does not reasonably provide enablement for other hyperproliferative diseases. (Office Action, pages 2-3). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims are broadly drawn to the treatment of any hyperproliferative disease, that it is not clear that all hyperproliferative diseases involve overexpression of Bcl-2 family proteins, that there is a limited number of working examples in the specification, and that the ability to treat all cancers with an anticancer agent is underdeveloped. (Office Action, pages 3-7).

Applicants respectfully disagree. Claims 30 and 31 have been canceled, rendering moot that portion of the rejection. Claim 1 as amended is directed to methods of treating or ameliorating a hyperproliferative disease selected from the group consisting of breast cancer, prostate cancer, colon cancer, lung cancer, and head and neck cancer. The present specification

provides working examples of the ability of gossypol compounds to treat each of these diseases. *See, e.g.*, for breast cancer Examples 11, 12, 16 and Table 8; for prostate cancer Examples 18-22 and Tables 9-11, 14, and 15; for colon cancer Example 23 and Table 12; for lung cancer Example 16 and Table 13; and for head and neck cancer Example 17. The Examiner has stated that the specification is enabling for the cancers demonstrated in the examples. Thus, the present claims are fully enabled.

Further, Applicants draw the Examiner's attention to the Declaration of Jon Theodore Holmlund, M.D. under 37 C.F.R. § 1.132 filed October 20, 2006 in U.S. Application No. 10/806,088 (copy attached hereto). The Declaration states that gossypol compounds are expected to have a therapeutic effect in a variety of cancers because apoptosis suppressing members of the Bcl-2 family are often strongly elevated in diverse cancers and gossypol compounds are known to bind to several different Bcl-2 family members. Thus, the declaration supports Applicants assertion that the present claims are fully enabled over their entire scope.

It is respectfully requested that the rejection of claims 1, 2, 27-41, and 43-45 under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 52-55, 60, 61, 78-80, 82-93, and 96 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Flack *et al.* (U.S. Patent No. 6,114,397) in view of Merck Manual of Diagnosis and Therapy. (Office Action, page 8). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

[i]t would have been obvious to one of ordinary skill in the art at the time of invention to employ both radiation and gossypol compounds of '397, as racemic or pure enantiomers, in a method and composition of treating cancer. It would have been obvious to one of ordinary skill in the art at the time of invention to optimize the therapeutic regimen of the cancer treatment employing the gossypol compounds and radiation.

(Office Action, page 9). The Examiner further acknowledges the unexpected synergistic benefits demonstrated in the present specification but alleges that the unexpected results are not commensurate with the scope of the subject matter claimed. (Office Action, page 11).

Applicants respectfully disagree. Claims 54, 60, 82, and 83 have been canceled solely to expedite prosecution, rendering that portion of the rejection moot. Claim 52 as amended is directed to methods of treating or ameliorating breast cancer or prostate cancer comprising administering (-)-gossypol and one or more second agent(s) selected from docetaxel, paclitaxel, and/or radiation, wherein the combination of (-)-gossypol and a second agent produces a synergistic effect with respect to one or more of tumor shrinkage, tumor loss, time to tumor progression, or survival. Flack *et al.* do not disclose any examples of combination treatment with (-)-gossypol and docetaxel, paclitaxel, and/or radiation, and therefore do not show a synergistic response to combination treatment with respect to one or more of tumor shrinkage, tumor loss, time to tumor progression, or survival. One of ordinary skill in the art reading Flack *et al.* would not have a reasonable expectation that the particular claimed combinations of (-)-gossypol with the specified anticancer agents or radiation produce a synergistic effect with

respect to the specified outcomes. Thus, there can be no *prima facie* case of obviousness of claim 52 and dependent claims 53, 78-80, 84-93, and 96 over the cited art.

In contrast, the present specification discloses the synergistic effects of combinations (-)-gossypol with docetaxel, paclitaxel, and radiation in treating or ameliorating breast cancer and prostate cancer. See, *e.g.*, Example 12 (breast cancer, (-)-gossypol with paclitaxel or docetaxel), Example 16 (breast cancer, (-)-gossypol with docetaxel), Example 18 (prostate cancer, (-)-gossypol with radiation), Example 19 (prostate cancer, (-)-gossypol with radiation), Example 20 (prostate cancer, (-)-gossypol with radiation), Example 22 (prostate cancer, (-)-gossypol with docetaxel), Table 8 (breast cancer, (-)-gossypol with docetaxel), Table 9 (prostate cancer, (-)-gossypol with docetaxel), Table 10 (prostate cancer, (-)-gossypol with docetaxel), Table 14 (prostate cancer, (-)-gossypol with radiation), and Table 15 (prostate cancer, (-)-gossypol with radiation). Applicants have clearly demonstrated that (-)-gossypol exhibits synergistic effects when combined with each of docetaxel, paclitaxel and radiation for the treatment of breast cancer and prostate cancer. The claims as amended are commensurate in scope with the unexpected synergistic results shown in the specification.

The Examiner alleges that the synergistic effect is not seen in all cases, pointing to Fig. 16 and the cell killing effects at doses of (-)-gossypol above 10 μ M (Office Action, page 11). Applicants respectfully disagree with the Examiner's interpretation of the data. Fig. 16 shows that doses of (-)-gossypol alone above 10 μ M kill greater than 90% MCF-7 breast cancer cells. The combination of (-)-gossypol at the same dose with paclitaxel (TAXOL) is only slightly better, which the Examiner alleges is an indication that the combination is not always synergistic.

The Examiner's interpretation is incorrect. Because nearly all of the cells are killed at these high doses of (-)-gossypol alone, there are not enough living cells available for a synergistic effect to be demonstrated when combining (-)-gossypol with paclitaxel. Thus, the datapoints at high doses of (-)-gossypol in Fig. 16 are not an example of lack of synergy.

Applicants assert that any alleged *prima facie* case of obviousness is overcome by the showing of unexpected synergy with the claimed combinations. It is respectfully requested that the rejection of claims 52-55, 60, 61, 78-80, 82-93, and 96 under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

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